

We claim:

1. A humanized immunoglobulin light chain comprising (i) variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin light chain variable region sequence set forth as SEQ ID NO:2, and (ii) a variable framework region from a human acceptor immunoglobulin light chain sequence, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 3D6 light chain variable region sequence, wherein the framework residue is selected from the group consisting of:
  - (a) a residue that non-covalently binds antigen directly;
  - (b) a residue adjacent to a CDR;
  - (c) a CDR-interacting residue; and
  - (d) a residue participating in the VL-VH interface.
2. A humanized immunoglobulin heavy chain comprising (i) variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin heavy chain variable region sequence set forth as SEQ ID NO:4, and (ii) a variable framework region from a human acceptor immunoglobulin heavy chain, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 3D6 heavy chain variable region sequence, wherein the framework residue is selected from the group consisting of:
  - (a) a residue that non-covalently binds antigen directly;
  - (b) a residue adjacent to a CDR;
  - (c) a CDR-interacting residue; and
  - (d) a residue participating in the VL-VH interface.
3. The light chain of claim 1, wherein a CDR-interacting residue is identified by modeling the 3D6 light chain based on the solved structure of 1CR9.
4. The light chain of claim 1, wherein a CDR-interacting residue is identified by modeling the 3D6 light chain based on the solved structure of 1NLD.

5. The heavy chain of claim 2, wherein a CDR-interacting residue is identified by modeling the 3D6 heavy chain based on the solved structure of 1OPG.

6. A humanized immunoglobulin light chain comprising (i) variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin light chain variable region sequence set forth as SEQ ID NO:2, and (ii) a variable framework region from a human acceptor immunoglobulin light chain sequence, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 3D6 light chain variable region sequence, wherein the framework residue is a residue capable of affecting light chain variable region conformation or function as identified by analysis of a three-dimensional model of the 3D6 immunoglobulin light chain variable region.

7. A humanized immunoglobulin heavy chain comprising (i) variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin heavy chain variable region sequence set forth as SEQ ID NO:4, and (ii) variable framework region from a human acceptor immunoglobulin heavy chain, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 3D6 heavy chain variable region sequence, wherein the framework residue is a residue capable of affecting heavy chain variable region conformation or function as identified by analysis of a three-dimensional model of the 3D6 immunoglobulin heavy chain variable region.

8. The light chain of claim 6, wherein the framework residue is selected from the group consisting of a residue capable of interacting with antigen, a residue proximal to the antigen binding site, a residue capable of interacting with a CDR, a residue adjacent to a CDR, a residue within 6 Å of a CDR residue, a canonical residue, a vernier zone residue, an interchain packing residue, a rare residue, and a glycosylation site residue on the surface of the structural model.

9. The heavy chain of claim 7, wherein the framework residue is selected from the group consisting of a residue capable of interacting with antigen, a residue

proximal to the antigen binding site, a residue capable of interacting with a CDR, a residue adjacent to a CDR, a residue within 6 Å of a CDR residue, a canonical residue, a vernier zone residue, an interchain packing residue, an unusual residue, and a glycosylation site residue on the surface of the structural model.

5

10. The light chain of claim 6 or 8, wherein the framework residue is identified by modeling the 3D6 light chain based on the solved structure of 1CR9.

11. The light chain of claim 6 or 8, wherein the frame work residue is identified by modeling the 3D6 light chain based on the solved structure of 1NLD.

12. The heavy chain of claim 7 or 9, wherein the framework residue is identified by modeling the 3D6 heavy chain based on the solved structure of 1OPG.

13. A humanized immunoglobulin light chain comprising (i) variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin light chain variable region sequence set forth as SEQ ID NO:2, and (ii) a variable framework region from a human acceptor immunoglobulin light chain, provided that at least one framework residue selected from the group consisting of L1, L2, L36 and L46 (Kabat numbering convention) is substituted with the corresponding amino acid residue from the mouse 3D6 light chain variable region sequence.

14. A humanized immunoglobulin heavy chain comprising (i) variable region complementarity determining regions from the 3D6 heavy chain variable region sequence set forth as SEQ ID NO:4, and (ii) a variable framework regions from a human acceptor immunoglobulin heavy chain, provided that at least one framework residue selected from the group consisting of H49, H93 and H94 (Kabat numbering convention) is substituted with the corresponding amino acid residue from the mouse 3D6 heavy chain variable region sequence.

30

15. The light chain of any one claims 1, 3, 4, 6, 8, 10, 11 and 13, wherein the human acceptor light chain is of the subtype kappa II (Kabat convention).

16. The heavy chain of any one claims 2, 5, 7, 9, 12 and 14, wherein the human acceptor heavy chain is of the subtype III (Kabat convention).

17. The light chain of claim 15, wherein the human acceptor light chain is selected from the group consisting of Kabat ID 019230, Kabat ID 005131, Kabat ID 005058, Kabat ID 005057, Kabat ID 005059, Kabat ID U21040 and Kabat ID U41645.

18. The light chain of claim 15, wherein the human acceptor light chain is Kabat ID 019230.

19. The heavy chain of claim 16, wherein the human acceptor heavy chain is selected from the group consisting of Kabat ID 045919, Kabat ID 000459, Kabat ID 000553, Kabat ID 000386 and Kabat ID M23691.

20. The heavy chain of claim 16, wherein the human acceptor heavy chain is Kabat ID 045919.

21. The light chain of any one of claims 1, 3, 4, 6, 8, 10, 11, 13, 15, 17 and 18, wherein at least one rare human framework residue is substituted with an amino acid residue which is common for human variable light chain sequences at that position.

22. The light chain of claim 1, 3, 4, 6, 8, 10, 11, 13, 15, 17 and 18, wherein at least one rare human framework residue is substituted with a corresponding amino acid residue from a germline variable light chain sequence.

23. The light chain of claim 22, wherein the germline variable light chain sequence is selected from the group consisting of A1, A17, A18, A2, and A19.

24. The heavy chain of any one of claims 2, 5, 7, 9, 12, 14, 16, 19 and 20, wherein at least one rare human framework residue is substituted with an amino acid

residue which is common for human variable heavy chain sequences at that position.

A3 5 25. The heavy chain of any one of claims 2, 5, 7, 9, 12, 14, 16, 19 and 20, wherein at least one rare human framework residue is substituted with a corresponding amino acid residue from a germline variable heavy chain sequence.

10 26. The heavy chain of claim 25, wherein the germline variable heavy chain sequence is selected from the group consisting of VH3-48, VH3-23, VH3-7, VH3-21 and VH3-11.

27. The heavy chain of claim 25, wherein the germline variable heavy chain sequence is VH3-23.

15 A3 28. The light chain of any one of claims 21-23, wherein the rare framework residue is selected based on occurrence at that position in less than 10% of human light chain variable region sequences in the light chain variable region subgroup, and the common residue is selected based on an occurrence at that position in greater than 50% of sequences in the light chain variable region subgroup.

20 29. The heavy chain of any one of claims 24-26, wherein the rare framework residue is selected based on occurrence at that position in less than 10% of human heavy chain variable region sequences in the heavy chain variable region subgroup, and the common residue is selected based on an occurrence at that position in greater than 50% of sequences in the heavy chain variable region subgroup.

30 30. A light chain comprising the complementarity determining regions (CDRs) and variable region framework residues L1, L2, L36 and L46 (Kabat numbering convention) from the monoclonal antibody 3D6 light chain, wherein the remainder of the light chain is from a human immunoglobulin.

31. A heavy chain comprising the complementarity determining regions (CDRs) and variable framework residues H49, H93 and H94 (Kabat numbering convention) from the monoclonal antibody 3D6 heavy chain, wherein the remainder of the heavy chain is from a human immunoglobulin.

5

32. A humanized immunoglobulin comprising the light chain of any one of claims 1, 3, 4, 6, 8, 10, 11, 13, 15, 17 and 18, and the heavy chain of any one of claims 2, 5, 7, 9, 12, 14, 16, 19 and 20, or antigen binding fragment of said immunoglobulin.

10

33. The immunoglobulin or antigen binding fragment of claim 32, which specifically binds to beta amyloid peptide ( $A\beta$ ) with a binding affinity of at least  $10^7 M^{-1}$ .

15

34. The immunoglobulin or antigen binding fragment of claim 32, which specifically binds to beta amyloid peptide ( $A\beta$ ) with a binding affinity of at least  $10^8 M^{-1}$ .

20

35. The immunoglobulin or antigen binding fragment of claim 32, which specifically binds to beta amyloid peptide ( $A\beta$ ) with a binding affinity of at least  $10^9 M^{-1}$ .

25

36. The immunoglobulin or antigen binding fragment of claim 32, wherein the heavy chain isotype is  $\gamma 1$ .

37. The immunoglobulin or antigen binding fragment of claim 32, which binds to both soluble beta amyloid peptide ( $A\beta$ ) and aggregated  $A\beta$ .

30

38. The immunoglobulin of claim 37, wherein the soluble beta amyloid peptide ( $A\beta$ ) is disaggregated  $A\beta$ .

39. The immunoglobulin or antigen binding fragment of claim 32, which mediates phagocytosis of beta amyloid peptide ( $A\beta$ ).

40. The immunoglobulin or antigen binding fragment of claim 32, which crosses the blood-brain barrier in a subject.

5 41. The immunoglobulin or antigen binding fragment of claim 32, which reduces both beta amyloid peptide ( $A\beta$ ) burden and neuritic dystrophy in a subject.

42. A humanized immunoglobulin comprising a humanized heavy chain and a humanized light chain, wherein

10

(a) the humanized light chain comprises three complementarity determining regions (CDR1, CDR2 and CDR3) having amino acid sequences from the corresponding complementarity determining regions of the mouse 3D6 immunoglobulin light chain variable domain designated SEQ ID NO:2, and a variable region framework from a human light chain variable region framework sequence provided that at least one position selected from a first group consisting of L1, L2, L36 and L46 (Kabat numbering convention) is occupied by the same amino acid residue present in the equivalent position of the mouse 3D6 immunoglobulin light chain variable region framework; and

15

20

(b) the humanized heavy chain comprises three complementarity determining regions (CDR1, CDR2 and CDR3) having amino acid sequences from the corresponding complementarity determining regions of the mouse 3D6 immunoglobulin heavy chain variable domain designated SEQ ID NO:4, and a variable region framework from a human heavy chain variable region framework sequence provided that at least one position selected from a second group consisting of H49, H93 and H94 (Kabat numbering convention) is occupied by the same amino acid residue present in the equivalent position of the mouse 3D6 immunoglobulin heavy chain variable region framework;

25

30

wherein the humanized immunoglobulin specifically binds to beta amyloid peptide ( $A\beta$ ) with a binding affinity of at least  $10^7 \text{ M}^{-1}$ , wherein the 3D6

immunoglobulin has the light chain with a variable domain designated SEQ ID NO:2 and the heavy chain with a variable domain designated SEQ ID NO: 4.

43. The humanized immunoglobulin of claim 42, wherein human light chain  
5 variable region framework is from a kappa light chain variable region.

44. The humanized immunoglobulin of claim 42, wherein human heavy  
chain variable region framework is from an IgG1 heavy chain variable region.

10 45. The humanized immunoglobulin of claim 42, wherein the humanized  
light chain variable region framework is from a light chain selected from the group  
consisting of Kabat ID 019230, Kabat ID 005131, Kabat ID 005058, Kabat ID 005057,  
Kabat ID 005059, Kabat ID U21040 and Kabat ID U41645.

15 46. The humanized immunoglobulin of claim 42, wherein the humanized  
heavy chain variable region framework is from a heavy chain selected from the group  
consisting of Kabat ID 045919, Kabat ID 000459, Kabat ID 000553, Kabat ID 000386  
and Kabat ID M23691.

20 47. The humanized immunoglobulin of claim 42, wherein the humanized  
light chain variable region framework is identical to the Kabat ID 019230 light chain  
variable region framework sequence except for the positions from the first group, and  
the heavy chain variable region framework is identical to the Kabat ID 045919 heavy  
chain variable region framework sequence except for the positions from the second  
25 group.

48. The humanized immunoglobulin of claim 42, wherein the humanized light  
chain comprises complementarity determining regions that are identical to the  
corresponding complementarity determining regions of the mouse 3D6 heavy chain, and  
30 the humanized heavy chain comprises complementarity determining regions that are  
identical to the corresponding complementarity determining regions of the mouse 3D6  
heavy chain.



49. A humanized antibody comprising the complementarity determining regions (CDR1, CDR2 and CDR3) of the 3D6 variable light chain sequence set forth as SEQ ID NO:2.

5

50. A humanized antibody comprising the complementarity determining regions (CDR1, CDR2 and CDR3) of the 3D6 variable heavy chain sequence set forth as SEQ ID NO:4.

10

51. A humanized antibody, or antigen-binding fragment thereof, which specifically binds to beta amyloid peptide (A $\beta$ ), comprising a variable region comprising complementarity determining regions (CDRs) corresponding to CDRs from the mouse 3D6 antibody.

15

52. A humanized antibody which binds beta amyloid peptide (A $\beta$ ) with an affinity of at least  $10^7$  M<sup>-1</sup> comprising:

(a) a light chain variable domain comprising murine 3D6 complementarity determining region (CDR) amino acid residues and human VL subgroup II variable domain framework region (FR) amino acid residues; and

20

(b) a heavy chain variable domain comprising murine 3D6 complementarity determining region (CDR) amino acid residues and human VH subgroup III variable domain framework region (FR) amino acid residues.

25

53. A chimeric immunoglobulin comprising variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin variable region sequences set forth as SEQ ID NO:2 or SEQ ID NO:4, and variable framework regions from a human acceptor immunoglobulin.

30

54. An immunoglobulin, or antigen-binding fragment thereof, comprising a variable heavy chain region as set forth in SEQ ID NO:8 and a variable light chain region as set forth in SEQ ID NO:5.

55. An immunoglobulin, or antigen-binding fragment thereof, comprising a variable heavy chain region as set forth in SEQ ID NO:12 and a light chain region as set forth in SEQ ID NO:11.

5 56. An immunoglobulin comprising a variable heavy chain region as set forth in SEQ ID NO:8, a variable light chain region as set forth in SEQ ID NO:5, and constant regions from IgG1.

10 57. An immunoglobulin comprising a variable heavy chain region as set forth in SEQ ID NO:12, a light chain region as set forth in SEQ ID NO:11, and constant regions from IgG1.

15 ~~58. A method of preventing or treating an amyloidogenic disease in a patient, comprising administering to the patient an effective dosage of the humanized immunoglobulin of any one of claims 32-52.~~

20 ~~59. A method of preventing or treating Alzheimer's disease in a patient, comprising administering to the patient an effective dosage of the humanized immunoglobulin of any one of claims 32-52.~~

~~60. The method of claim 59, wherein the effective dosage of humanized immunoglobulin is 1 mg/kg body weight.~~

25 ~~61. The method of claim 59, wherein the effective dosage of humanized immunoglobulin is 10 mg/kg body weight.~~

~~62. A pharmaceutical composition comprising the immunoglobulin of any one of claims 32-52 and a pharmaceutical carrier.~~

30 ~~63. An isolated polypeptide comprising a fragment of SEQ ID NO:2 selected from the group consisting of amino acids 24-39 of SEQ ID NO:2, amino acids 55-61 of SEQ ID NO:2 and amino acids 94-102 of SEQ ID NO:2.~~

64. An isolated polypeptide comprising amino acids 24-39 of SEQ ID NO:2, amino acids 55-61 of SEQ ID NO:2 and amino acids 94-102 of SEQ ID NO:2.

5 65. An isolated polypeptide comprising a fragment of SEQ ID NO:4 selected from the group consisting of amino acids 31-35 of SEQ ID NO:4, amino acids 50-66 of SEQ ID NO:4 and amino acids 99-107 of SEQ ID NO:4.

10 66. An isolated polypeptide comprising amino acids 31-35 of SEQ ID NO:4, amino acids 50-66 of SEQ ID NO:4 and amino acids 99-107 of SEQ ID NO:4.

67. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:2.

15 68. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:4.

69. A variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, said variant comprising at least one conservative amino acid substitution, wherein the variant retains the ability to direct specific binding to beta amyloid peptide ( $A\beta$ ) with a binding affinity of at least  $10^7 M^{-1}$ .

70. A variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:4, said variant comprising at least one conservative amino acid substitution, wherein the variant retains the ability to specifically bind beta amyloid peptide ( $A\beta$ ) with a binding affinity of at least  $10^7 M^{-1}$ .

71. An isolated polypeptide comprising residues 1-112 of the amino acid sequence of SEQ ID NO:2 or comprising residues 1-119 of the amino acid sequence of SEQ ID NO:4.

72. An isolated nucleic acid molecule encoding the light chain of any one of claims 1, 3, 4, 6, 8, 10, , 11, 13, 15, 17 and 18.

73. An isolated nucleic acid molecule encoding the heavy chain of any one of claims 2, 5, 7, 9, 12, 14, 16, 19 and 20.

74. An isolated nucleic acid molecule encoding the polypeptide of any one of claims 64-71.

75. An isolated nucleic acid molecule encoding the immunoglobulin of any one of claims 32-57.

76. An isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1 or 3.

77. A vector comprising the nucleic acid molecule of any of claims 72-76.

78. A host cell comprising the nucleic acid molecule of any of claims 72-76.

79. A method of producing an antibody, or fragment thereof, comprising culturing the host cell of claim 45 under conditions such that the antibody or fragment is produced and isolating said antibody from the host cell or culture.

80. A method of producing an antibody or fragment thereof, said method comprising culturing a host cell that expresses a nucleic acid molecule encoding said antibody or fragment under conditions such that the antibody or fragment is produced, and isolating said antibody or fragment from the host cell or culture, wherein said antibody or fragment comprises amino acids 24-39 of SEQ ID NO:2, amino acids 55-61 of SEQ ID NO:2 and amino acids 94-102 of SEQ ID NO:2.

81. A method of producing an antibody or fragment thereof, said method comprising culturing a host cell that expresses a nucleic acid molecule encoding said

antibody or fragment, under conditions such that the antibody or fragment is produced, and isolating said antibody from the host cell or culture, wherein said antibody or fragment comprises amino acids 31-35 of SEQ ID NO:4, amino acids 50-66 of SEQ ID NO:4 and amino acids 99-112 of SEQ ID NO:4.

5

82. A method for identifying residues amenable to substitution in a humanized 3D6 immunoglobulin variable framework region, comprising modeling the three-dimensional structure of the 3D6 variable region based on a solved immunoglobulin structure and analyzing said model for residues capable of affecting 3D6 immunoglobulin variable region conformation or function, such that residues amenable to substitution are identified.

10

83. Use of the variable region sequence set forth as SEQ ID NO:2 or SEQ ID NO:4, or any portion thereof, in producing a three-dimensional image of a 3D6 immunoglobulin, 3D6 immunoglobulin chain, or domain thereof.

15

84. A humanized immunoglobulin light chain comprising (i) variable region complementary determining regions (CDRs) from the 10D5 immunoglobulin light chain variable region sequence set forth as SEQ ID NO:14, and (ii) a variable framework region from a human acceptor immunoglobulin light chain sequence, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 10D5 light chain variable region sequence, wherein the framework residue is selected from the group consisting of:

20

- (a) a residue that non-covalently binds antigen directly;
- (b) a residue adjacent to a CDR;
- (c) a CDR-interacting residue; and
- (d) a residue participating in the VL-VH interface.

25

85. A humanized immunoglobulin heavy chain comprising (i) variable region complementary determining regions (CDRs) from the 10D5 immunoglobulin heavy chain variable region sequence set forth as SEQ ID NO:16, and (ii) a variable framework region from a human acceptor immunoglobulin heavy chain, provided that at least one

30

framework residue is substituted with the corresponding amino acid residue from the mouse 10D5 heavy chain variable region sequence, wherein the framework residue is selected from the group consisting of:

- (a) a residue that non-covalently binds antigen directly;
- 5 (b) a residue adjacent to a CDR;
- (c) a CDR-interacting residue; and
- (d) a residue participating in the VL-VH interface.

86. The light chain of claim 84, wherein a CDR-interacting residue is identified by modeling the 10D5 light chain based on the solved structure of a murine immunoglobulin light chain that shares at least 70% sequence identity with the 10D5 light chain.

87. The light chain of claim 84, wherein a CDR-interacting residue is identified by modeling the 10D5 light chain based on the solved structure of a murine immunoglobulin light chain that shares at least 80% sequence identity with the 10D5 light chain.

88. The light chain of claim 84, wherein a CDR-interacting residue is identified by modeling the 10D5 light chain based on the solved structure of a murine immunoglobulin light chain that shares at least 90% sequence identity with the 10D5 light chain.

89. The heavy chain of claim 85, wherein a CDR-interacting residue is identified by modeling the 10D5 heavy chain based on the solved structure of a murine immunoglobulin heavy chain that shares at least 70% sequence identity with the 10D5 heavy chain.

90. The heavy chain of claim 85, wherein a CDR-interacting residue is identified by modeling the 10D5 heavy chain based on the solved structure of a murine immunoglobulin heavy chain that shares at least 80% sequence identity with the 10D5 heavy chain.

91. The heavy chain of claim 85, wherein a CDR-interacting residue is identified by modeling the 10D5 heavy chain based on the solved structure of a murine immunoglobulin heavy chain that shares at least 90% sequence identity with the 10D5 heavy chain.

92. A humanized immunoglobulin light chain comprising (i) variable region complementary determining regions (CDRs) from the 10D5 immunoglobulin light chain variable region sequence set forth as SEQ ID NO:14, and (ii) a variable framework region from a human acceptor immunoglobulin light chain sequence, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 10D5 light chain variable region sequence, wherein the framework residue is a residue capable of affecting light chain variable region conformation or function as identified by analysis of a three-dimensional model of the 10D5 immunoglobulin light chain variable region.

93. A humanized immunoglobulin heavy chain comprising (i) variable region complementary determining regions (CDRs) from the 10D5 immunoglobulin heavy chain variable region sequence set forth as SEQ ID NO:16, and (ii) a variable framework region from a human acceptor immunoglobulin heavy chain, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 10D5 heavy chain variable region sequence, wherein the framework residue is a residue capable of affecting heavy chain variable region conformation or function as identified by analysis of a three-dimensional model of the 10D5 immunoglobulin heavy chain variable region.

94. The light chain of claim 92, wherein the framework residue is selected from the group consisting of a residue capable of interacting with antigen, a residue proximal to the antigen binding site, a residue capable of interacting with a CDR, a residue adjacent to a CDR, a residue within 6 Å of a CDR residue, a canonical residue, a vernier zone residue, an interchain packing residue, a rare residue, and a glycosylation site residue on the surface of the structural model.

95. The heavy chain of claim 93, wherein the framework residue is selected from the group consisting of a residue capable of interacting with antigen, a residue proximal to the antigen binding site, a residue capable of interacting with a CDR, a residue adjacent to a CDR, a residue within 6 Å of a CDR residue, a canonical residue, a vernier zone residue, an interchain packing residue, an unusual residue, and a glycosylation site residue on the surface of the structural model.

96. The light chain of claim 92 or 94, wherein the framework residue is identified by modeling the 10D5 light chain based on the solved structure of a murine immunoglobulin light chain that shares at least 70% sequence identity with the 10D5 light chain.

97. The light chain of claim 92 or 94, wherein the framework residue is identified by modeling the 10D5 light chain based on the solved structure of a murine immunoglobulin light chain that shares at least 80% sequence identity with the 10D5 light chain.

98. The light chain of claim 92 or 94, wherein the framework residue is identified by modeling the 10D5 light chain based on the solved structure of a murine immunoglobulin light chain that shares at least 90% sequence identity with the 10D5 light chain.

99. The heavy chain of claim 93 or 95, wherein the framework residue is identified by modeling the 10D5 heavy chain based on the solved structure of a murine immunoglobulin heavy chain that shares at least 70% sequence identity with the 10D5 heavy chain.

100. The heavy chain of claim 93 or 95, wherein the framework residue is identified by modeling the 10D5 heavy chain based on the solved structure of a murine immunoglobulin heavy chain that shares at least 80% sequence identity with the 10D5 heavy chain.



101. The heavy chain of claim 93 or 95, wherein the framework residue is identified by modeling the 10D5 heavy chain based on the solved structure of a murine immunoglobulin heavy chain that shares at least 90% sequence identity with the 10D5 heavy chain..

102. The light chain of any one of claims 84, 86-88, 92, 94 and 96-98, wherein at least one rare human framework residue is substituted with an amino acid residue which is common for human variable light chain sequences at that position.

103. The light chain of any one of claims 84, 86-88, 92, 94 and 96-98, wherein at least one rare human framework residue is substituted with a corresponding amino acid residue from a germline variable light chain sequence.

104. The light chain of claim 103, wherein the germline variable light chain sequence is that of an immunoglobulin sharing at least 70% identity with the variable light chain sequence of sequence identity.

105. The light chain of claim 103, wherein the germline variable light chain sequence is that of an immunoglobulin sharing at least 80% identity with the variable light chain sequence of sequence identity.

106. The light chain of claim 103, wherein the germline variable light chain sequence is that of an immunoglobulin sharing at least 90% identity with the variable light chain sequence of sequence identity.

107. The heavy chain of any one of claims 85, 89-91, 93 and 99-101, wherein at least one rare human framework residue is substituted with an amino acid residue which is common for human variable heavy chain sequences at that position.

108. The heavy chain of any one of claims 85, 89-91, 93 and 99-101, wherein at least one rare human framework residue is substituted with a corresponding amino acid residue from a germline variable heavy chain sequence.

5 109. The heavy chain of claim 108, wherein the germline variable heavy chain sequence is that of or is sharing of at least 70% identity with the variable heavy chain sequence of SEQ ID NO:16.

10 110. The heavy chain of claim 108, wherein the germline variable heavy chain sequence is that of or is sharing of at least 80% identity with the variable heavy chain sequence of sequence identity no. 16.

15 111. The heavy chain of claim 108, wherein the germline variable heavy chain sequence is that of or is sharing of at least 90% identity with the variable heavy chain sequence of sequence identity no. 16.

20 112. The light chain of any one of claims 102-106, wherein the rare framework residue is selected based on occurrence at that position in less than 10% of human light chain variable region sequences in the light chain variable region subgroup, and the common residue is selected based on an occurrence at that position in greater than 50% of sequences in the light chain variable region subgroup.

25 113. The heavy chain of any one of claims 107-111, wherein the rare framework residue is selected based on occurrence at that position in less than 10% of human heavy chain variable region sequences in the heavy chain variable region subgroup, and the common residue is selected based on an occurrence at that position in greater than 50% of sequences in the heavy chain variable region subgroup.

30 *not A10* 114. A humanized immunoglobulin comprising the light chain of any one of claims 84, 86-88, 92, 94 and 96-98, and the heavy chain of any one of claims 85, 89-91, and 93 and 99-101, or antigen-binding fragment of said immunoglobulin.

115. The immunoglobulin or antigen binding fragment of claim 114, which specifically binds to beta amyloid peptide (A $\beta$ ) with a binding affinity of at least  $10^{-7}$  M.

116. The immunoglobulin or antigen binding fragment of claim 114, which specifically binds to beta amyloid peptide (A $\beta$ ) with a binding affinity of at least  $10^{-8}$  M.

117. The immunoglobulin or antigen binding fragment of claim 114, which specifically binds to beta amyloid peptide (A $\beta$ ) with a binding affinity of at least  $10^{-9}$  M.

118. The immunoglobulin or antigen binding fragment of claim 114, wherein the heavy chain isotype is  $\gamma 1$ .

119. The immunoglobulin or antigen binding fragment of claim 114, which binds to aggregated beta amyloid peptide (A $\beta$ ).

120. The immunoglobulin or antigen binding fragment of claim 114, which mediates phagocytosis of beta amyloid peptide (A $\beta$ ).

121. The immunoglobulin or antigen binding fragment of claim 114, which crosses the blood-brain barrier in a subject.

122. The immunoglobulin or antigen binding fragment of claim 114, which reduces beta amyloid peptide (A $\beta$ ) plaque burden in a subject.

123. A humanized immunoglobulin comprising a humanized heavy chain and a humanized light chain, wherein

(a) the humanized light chain comprises three complementary determining regions (CDR1, CDR2 and CDR3) having amino acid sequences from the corresponding complementarily determining regions of the mouse 10D5 immunoglobulin light chain variable domain designated SEQ ID NO:14, and a variable region framework from a human light chain variable region framework

sequence provided that at least one framework residue selected from the group consisting of a canonical residue, a vernier residue, a packing residue and a rare residue, is occupied by the same amino acid residue present in the equivalent position of the mouse 10D5 immunoglobulin light chain variable region framework; and

(b) the humanized heavy chain comprises three complementary determining regions (CDR1, CDR2 and CDR3) having amino acid sequences from the corresponding complementary determining regions of the mouse 10D5 immunoglobulin heavy chain variable domain designated SEQ ID NO:16, and a variable region framework from a human heavy chain variable region framework sequence provided that at least one framework residue selected from a second group consisting of a canonical residue, a vernier residue, a packing residue and a rare residue, is occupied by the same amino acid residue present in the equivalent position of the mouse 10D5 immunoglobulin heavy chain variable region framework;

wherein the humanized immunoglobulin specifically binds to beta amyloid peptide ("A $\beta$ ") with a binding affinity of at least  $10^{-7}$  M, wherein the 10D5 immunoglobulin has the light chain with a variable domain designated SEQ ID NO:14 and the heavy chain with a variable domain designated SEQ ID NO:16.

124. The humanized immunoglobulin of claim 123, wherein human light chain variable region framework is from a kappa light chain variable region.

125. The humanized immunoglobulin of claim 123, wherein human heavy chain variable region framework is from an IgG1 heavy chain variable region.

126. The humanized immunoglobulin of claim 123, wherein the light chain variable region framework is from a human immunoglobulin light chain having at least 70% sequence identity with light chain sequence of the 10D5 immunoglobulin.

127. The humanized immunoglobulin of claim 123, wherein the heavy chain variable region framework is from a human immunoglobulin heavy chain having at least 70% sequence identity with heavy chain sequence of the 10D5 immunoglobulin..

5 128. The humanized immunoglobulin of claim 123, wherein the humanized light chain comprises complementary determining regions that are identical to the corresponding complementary determining regions of the mouse 10D5 heavy chain, and the humanized heavy chain comprises complementary determining regions that are identical to the corresponding complementary determining regions of the mouse 10D5 heavy chain.

129. A humanized antibody comprising the complementary determining regions (CDR1, CDR2 and CDR3) of the 10D5 variable light chain sequence set forth as SEQ ID NO:14.

15 130. A humanized antibody comprising the complementary determining regions (CDR1, CDR2 and CDR3) of the 10D5 variable heavy chain sequence set forth as SEQ ID NO:16.

20 131. A humanized antibody, or antigen-binding fragment thereof, which specifically binds to beta amyloid peptide (A $\beta$ ), comprising a variable region comprising complementary determining regions (CDRs) corresponding to CDRs from the mouse 10D5 antibody.

25 132. A chimeric immunoglobulin comprising variable region sequence substantially as set forth in SEQ ID NO:14 or SEQ ID NO:16, and constant region sequences from a human immunoglobulin.

30 *put in* 133. A method of preventing or treating an amyloidogenic disease in a patient, comprising administering to the patient an effective dosage of the humanized immunoglobulin of any one of claims 114-131.

134. A method of preventing or treating Alzheimer's disease in a patient, comprising administering to the patient an effective dosage of the humanized immunoglobulin of any one of claims 114-131.

5 135. The method of claim 134, wherein the effective dosage of humanized immunoglobulin is 1 mg/kg body weight.

136. The method of claim 134, wherein the effective dosage of humanized immunoglobulin is 10 mg/kg body weight.

10 137. A pharmaceutical composition comprising the immunoglobulin of any one of claims 114-131 and a pharmaceutical carrier.

138. An isolated polypeptide comprising a fragment of SEQ ID NO:2 selected from the group consisting of amino acids 24-39 of SEQ ID NO:2, amino acids 55-61 of SEQ ID NO:2 and amino acids 94-102 of SEQ ID NO:2.

139. An isolated polypeptide comprising amino acids 24-39 of SEQ ID NO:2, amino acids 55-61 of SEQ ID NO:2 and amino acids 94-102 of SEQ ID NO:2.

20 140. An isolated polypeptide comprising a fragment of SEQ ID NO:4 selected from the group consisting of amino acids 31-37 of SEQ ID NO:4, amino acids 52-67 of SEQ ID NO:4 and amino acids 100-112 of SEQ ID NO:4.

25 141. An isolated polypeptide comprising amino acids 31-37 of SEQ ID NO:4, amino acids 52-67 of SEQ ID NO:4 and amino acids 100-112 of SEQ ID NO:4.

142. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:14.

30 143. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:16.

144. A variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:14, said variant comprising at least one conservative amino acid substitution, wherein the variant retains the ability to specifically bind beta amyloid peptide (A $\beta$ ) with a binding affinity of at least  $10^{-7}$  M.

145. A variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:16, said variant comprising at least one conservative amino acid substitution, wherein the variant retains the ability to direct specific binding to beta amyloid peptide (A $\beta$ ) with a binding affinity of at least  $10^{-7}$  M.

146. An isolated polypeptide comprising residues 1-112 of the amino acid sequence of SEQ ID NO:14 or comprising residues 1-123 of the amino acid sequence of SEQ ID NO:16.

147. An isolated nucleic acid molecule encoding the light chain of any one of claims 84, 86-88, 92, 94 and 96-98.

148. An isolated nucleic acid molecule encoding the heavy chain of any one of claims 85, 89-91, 93 and 99-101.

149. An isolated nucleic acid molecule encoding the polypeptide of any one of claims 139-146.

150. An isolated nucleic acid molecule encoding the immunoglobulin of any one of claims 114-132.

151. An isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:13 or 15.

152. A vector comprising the nucleic acid molecule of any of claims 147-151.

151. ~~A5~~ 153. A host cell comprising the nucleic acid molecule of any of claims 147-151.

5 154. A method of producing an antibody, or fragment thereof, comprising culturing the host cell of claim 153 under conditions such that the antibody or fragment is produced and isolating said antibody from the host cell or culture.

10 155. A method of producing an antibody, or fragment thereof, said method comprising culturing a host cell that expresses a nucleic acid molecule encoding said antibody or fragment under conditions such that the antibody or fragment is produced, and isolating said antibody from the host cell or culture, wherein said antibody or fragment comprises amino acids 24-39 of SEQ ID NO:2, amino acids 55-61 of SEQ ID NO:2 and amino acids 94-102 of SEQ ID NO:2.

15 156. A method of producing an antibody, or fragment thereof, said method comprising culturing a host cell that expresses a nucleic acid molecule encoding said antibody or fragment under conditions such that the antibody or fragment is produced, and isolating said antibody from the host cell or culture, wherein said antibody or fragment comprises amino acids 31-37 of SEQ ID NO:4, amino acids 52-67 of SEQ ID  
20 NO:4 and amino acids 100-112 of SEQ ID NO:4.

25 157. A method for identifying residues amenable to substitution in a humanized 10D5 immunoglobulin variable framework region, comprising modeling the three-dimensional structure of the 10D5 variable region based on a solved immunoglobulin structure and analyzing said model for residues capable of affecting 10D5 immunoglobulin variable region conformation or function, such that residues amenable to substitution are identified.

30 158. Use of the variable region sequence set forth as SEQ ID NO:14 or SEQ ID NO:16, or any portion thereof, in producing a three-dimensional image of a 10D5 immunoglobulin, 10D5 immunoglobulin chain, or domain thereof.